Endothelin is an endogenous substance which directly or indirectly (by controlling liberation of various endogenous substances) induces sustained contraction or relaxation of vascular or non-vascular smooth muscles, and its excess production or excess secretion is believed to be one of pathogeneses for hypertension, pulmonary hypertension, Raynaud's disease, bronchial asthma, gastric ulcer, diabetes, arteriosclerosis, restenosis, acute renal failure, myocardial infarction, angina pectoris, cerebral vasospasm and cerebral infarction. Further, it is suggested that endothelin serves as an important mediator involved in diseases such as restenosis, prostatauxe, endotoxin shock, endotoxin-induced multiple organ failure or disseminated intravascular coagulation, and cyclosporin-induced renal failure or hypertension. Two endothelin receptors ET_A and ET_B are known so far and antagonists of these receptors have been shown to be potential drug targets.

EP 0526708 Al and WO 93/08799 Al are representative examples of patent applications disclosing non-peptidic compounds with alleged activity as endothelin receptor antagonists.

Tillyer et al. (U.S. Pat. No. 5,998,625) is directed to a process for preparing a key intermediate in the synthesis of an endothelin antagonist using a chiral additive to effect an asymmetric conjugate addition.

Tillyer et al. (U.S. Pat. No. 6,046,327) discloses the phosphate-mediated cyclization process in the preparation of an endothelin antagonist.

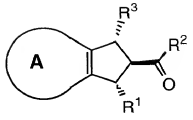
Ishikawa et al. (WO9505374) discloses fused heteroaromatic cyclopentene derivative having endothelin-antagonist activity.

Bradsher et al. (*J. Org. Chem.*, 46, 1384-1388 (1981), "Oxygen Heterocycles by the Parham Cyclialkylation") relates to the Parham cyclialkylation to form rings containing oxygen atom to afford 2,3-dihydrobenzofurans, 3,4-dihydro-2H-1-benzopyrans, or 2,3,4,5-tetrahydro-1-benzoxepins.

An object of the present invention is to develop a practical synthetic route to prepare an asymmetric endothelin receptor antagonist.

SUMMARY OF THE INVENTION

The present invention relates to a process for preparing a compound for an endothelin receptor antagonist of Formula I,



I

wherein:

represents:

(a) 5- or 6-membered heterocyclyl containing one to three double bonds, but at least one double bond and 1 to 3 heteroatoms selected from O, N and S, and the heterocyclyl is optionally substituted with one to three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, $(C_1\text{-}C_8)$-alkoxy, $(C_1\text{-}C_8)$-alkyl, $(C_2\text{-}C_8)$-alkenyl, $(C_2\text{-}C_8)$-alkynyl, $(C_3\text{-}C_8)$-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$;

(b) 5- or 6-membered carbocyclyl containing one or two double bonds, but at least one double bond, and the carbocyclyl is optionally substituted with one to three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, $(C_1\text{-}C_8)$-alkoxy, $(C_1\text{-}C_8)$-alkyl, $(C_2\text{-}C_8)$-alkenyl, $(C_2\text{-}C_8)$-alkynyl, $(C_3\text{-}C_8)$-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$; or

(c) aryl, wherein aryl is defined as phenyl or naphthyl, which is optionally substituted with one to three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, $(C_1\text{-}C_8)$-alkoxy, $(C_1\text{-}C_8)$-alkyl, $(C_2\text{-}C_8)$-alkenyl, $(C_2\text{-}C_8)$-alkynyl, $(C_3\text{-}C_8)$-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$, or when aryl is substituted on adjacent carbons they can form a 5- or 6-membered fused ring having one to three heteroatoms selected from O, N, and S, this ring being optionally substituted on carbon or nitrogen with one to three substituents selected from the group consisting of: H, OH, CO_2R^6, Br, Cl, F, I, CF_3, $N(R^7)_2$, $(C_1\text{-}C_8)$-alkoxy, $(C_1\text{-}C_8)$-alkyl, $(C_2\text{-}C_8)$-

alkenyl, (C_2-C_8)-alkynyl, (C_3-C_8)-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$;
and wherein (C_1-C_8)-alkoxy, (C_1-C_8)-alkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, or (C_3-C_8)-cycloalkyl substituent of aryl is further optionally substituted with one to three substituents
selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $OCPh_3$, $N(R^5)_2$, (C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$;

R^1 is:

(a) (C_1-C_8)-alkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, or (C_3-C_8)-cycloalkyl,

(b) aryl, wherein aryl as defined above, or

(c) heteroaryl, wherein heteroaryl is defined as a 5- or 6-membered aromatic ring containing one to three heteroatoms selected from O, N and S, and is optionally substituted with one to three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, (C_1-C_8)-alkoxy, (C_1-C_8)-alkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, (C_3-C_8)-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$;

R^2 is: OR^4 or $N(R^5)_2$;

R^3 is:

(a) (C_1-C_8)-alkyl,
(b) (C_2-C_8)-alkenyl,
(c) (C_2-C_8)-alkynyl,
(d) (C_3-C_7)-cycloalkyl,
(e) aryl, wherein aryl as defined above,
(f) heteroaryl, wherein heteroaryl as defined above
(g) -CHO,
(h) -CO-(C_1-C_8)-alkyl,
(i) -CO-aryl,
(j) -CO-heteroaryl, or